Complete Summary

GUIDELINE TITLE

Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians.

BIBLIOGRAPHIC SOURCE(S)

Qaseem A, Snow V, Cross JT Jr, Forciea MA, Hopkins R Jr, Shekelle P, Adelman A, Mehr D, Schellhase K, Campos-Outcalt D, Santaguida P, Owens DK, American College of Physicians/American Academy of Family Physicians Panel on Dementia. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008 Mar 4;148(5):370-8. [63 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Dementia including:

- Alzheimer disease
- Vascular dementia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Geriatrics
Internal Medicine
Neurology
Psychiatry

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To present the available evidence on current pharmacologic treatment of dementia

TARGET POPULATION

Adults 18 years or older with a diagnosis of dementia

INTERVENTIONS AND PRACTICES CONSIDERED

Use of cholinesterase inhibitors and memantine for selected patients

MAJOR OUTCOMES CONSIDERED

- Cognition
- Global function
- Behavior/mood
- Quality of life/activities of daily living
- Caregiver burden
- Adverse effects of medications
- Rate of institutionalization
- Mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): These recommendations are based on the systematic evidence review by Raina and

colleagues and the Agency for Healthcare Research and Quality–sponsored McMaster University Evidence-based Practice Center evidence report (see the "Availability of Companion Documents" field).

Search and Selection

The authors of the evidence report searched the Cochrane Central Register of Controlled Trials, MEDLINE, PREMEDLINE, EMBASE, Allied and Complementary Medicine Database, CINAHL, AgeLine, and PsycINFO for relevant evidence published in English from January 1986 through November 2006. The bibliographies of retrieved papers were also reviewed.

All populations with major dementias (including Alzheimer disease, vascular dementia, and Parkinson dementia) and mild cognitive impairment were included. Only parallel randomized, controlled trials that compared a cholinesterase inhibitor or memantine with placebo or another drug were eligible. Crossover trials were excluded because of potential bias due to period effects or period-by-treatment interaction. The content-expert panel reached consensus and established that eligible studies also had to have a minimum modified Jadad score of 3 of 5 (original scale), indicating moderate study quality. Study outcomes primarily encompassed 4 broad domains: cognition, global function, behavior, and quality of life (including activities of daily living [ADLs] and caregiver burden). Most clinical outcomes were classified within these 4 domains; other outcomes were rate of institutionalization, mortality, or adverse events.

Eligibility criteria for studies were: 1) patients with dementia who were 18 years of age or older; 2) diagnosis of dementia using International Classification of Diseases, Ninth or Tenth Revision, and Diagnostic and Statistical Manual of Mental Disorders III, III-R, or IV and various other criteria; 3) interventions restricted to pharmacologic agents, including food supplements administered at least once daily; 4) parallel randomized, controlled trials in English of any sample size; and 5) a score of 3 or greater on the modified Jadad scale. Details about inclusion and exclusion criteria are available in the evidence review (see the "Availability of Companion Documents" field).

NUMBER OF SOURCE DOCUMENTS

96 publications representing 59 unique studies were eligible for review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

This guideline grades the evidence and recommendations by using the American College of Physicians' clinical practice guidelines grading system adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup (see "Rating Scheme for the Strength of the Recommendations" field, below).

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data Abstraction and Quality Assessment

Two independent reviewers abstracted data from and assessed the quality of all studies that met the eligibility criteria. The modified Jadad scale (which includes additional domains that concern collection of adverse events, description of statistical analysis, and reporting of eligibility criteria) and a checklist for the quality of reporting of adverse events were used to evaluate methodological quality; the latter measures included questions on frequency of reporting harms, withdrawals, and method of collection.

Data Synthesis and Statistical Analysis

Evaluation of benefit was based on reported changes in the principal outcome within the domains of interest.

Within the domain of cognition, the authors considered the Alzheimer's Disease Assessment Scale (ADAS) consisting of the cognitive subscale (ADAS-cog), noncognitive subscale (ADAS-noncog), and total ADAS score (ADAS-tot), the Mini-Mental State Examination (MMSE) (or the standardized MMSE version), and the Severe Impairment Battery (SIB) to be commonly used measures that have established properties and are scored by a trained evaluator or clinician.

For the domain of global function, a commonly used outcome is the clinician-based impression of change (CIBIC), with caregiver input (CIBIC-plus) and other modified versions (New York University–CIBIC-plus, clinician's global impression of change [CGIC], Alzheimer's Disease Cooperative Study CGIC, and clinician interview–based impression). Because the CIBIC-plus is a global rating by clinicians, any change in score is considered clinically significant.

To evaluate adverse effects, a standardized instrument was used that assessed rates of withdrawals due to adverse effects, the method (active versus passive and standardized versus nonstandardized approaches) and frequency of collection of harms, and the definition and collection of serious and severe harms. A priori, specific events (nausea, diarrhea, dizziness, accidental injury, agitation, urinary disorder, serious adverse events) were selected and expressed as a percentage for each study. Where 2 or more studies provided sufficient information, the summary estimate was calculated for the specific adverse event evaluated.

The reviewers used standard meta-analytic techniques to estimate effect sizes for each drug in studies with the same outcomes. The effect measure selected varied according to the manner in which the outcome was reported and included change scores or, for dichotomous data, relative risks (RRs). Reasonableness of pooling was assessed on clinical and biological grounds in terms of clinical heterogeneity

(drugs, similarity of populations, and outcomes); therefore, meta-analysis was not appropriate for all outcomes. Summary estimates were not included when studies provided only end point scores. Similarly, studies were excluded that did not provide a measure of variance for outcomes when computing summary estimates.

When meta-analyses were undertaken, the weighted mean difference (WMD) was selected as the pooled estimate instead of the standardized mean difference. When only the proportions of patients whose condition improved or worsened were reported, the RR was used as a measure of the summary effect size. In all meta-analyses, a random- effects model was used; tests for statistical heterogeneity were based on the chi-square statistic and the I^2 statistic. In some cases, estimates of mean changes in the study outcomes used for the meta-analyses were based on best estimates derived from figures in the citations.

Refer to the Evidence Review report (see the "Availability of Companion Documents" field) for additional information on the methods used to analyze the evidence.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Guideline developers systematically reviewed the literature to address the following questions:

- Does pharmacologic treatment of dementia with any of the five U.S. Food and Drug Administration (FDA)-approved drugs improve cognitive symptoms and outcomes?
- What is the evidence for efficacy of the cholinergic neurotransmitter–modifying agents, such as cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine) and the noncholinergic neurotransmitter– or neuropeptide-modifying agent (memantine) in the treatment of dementia?

The guideline developers reviewed the evidence addressing the questions posed by this report and based the recommendations on the gathered evidence.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

American College of Physicians' Clinical Practice Guidelines Grading System*		
Quality of Evidence	**Strength of Recommendation**	
	Benefits	Benefits

American College of Physicians' Clinical Practice Guidelines Grading System*		
Quality of Evidence	**Strength of Recommendation**	
	Clearly Outweigh Risks and Burden **OR** Risks and Burden Clearly Outweigh Benefits	Finely Balanced with Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I recommendation	

*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

COST ANALYSIS

Published cost analyses were reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was approved by the American College of Physicians' Board of Regents on 16 April 2007 and by the American Academy of Family Physicians' Board of Directors on 13 June 2007.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The strength of evidence (high, moderate, low, insufficient evidence to determine benefits or risks) and strength of recommendations (strong, weak, I recommendation) are defined at the end of the "Major Recommendations."

Recommendation 1: *Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment.* (**Grade: weak recommendation, moderate-quality evidence.**)

The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient. In particular, in more advanced dementia, family or other decision makers may not view stabilization or slowing of decline as a desirable goal if quality of life is judged to be poor. All of the drugs have known adverse events, and the decision to manage patients with dementia should balance harms against modest or even no benefit. Although the evidence shows statistically significant benefits of treatment with some cholinesterase inhibitors and memantine for all kinds of dementia, these benefits, on average, are not clinically significant for cognition and are modest for global assessments. However, limited evidence suggests, but does not demonstrate conclusively, that a subgroup of patients achieves clinically important improvements. Currently, there is no way to predict which patients might have a clinically important response. Therefore, the evidence does not support prescribing these medications for every patient with dementia.

Evidence is insufficient to determine the optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months on the basis of duration of trials. This effect could be an improvement or stabilization. In addition, no evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. However, if slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate.

Recommendation 2: *Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia.* (**Grade: weak recommendation, low-quality evidence.**)

Because few trials compare one drug with another, evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia. Therefore, tolerability, adverse effect profile, ease of use, and cost of medication are reasonable criteria to help select a treatment. For example, when the benefits and harms related to a drug are being evaluated, the severe side effects associated with tacrine make it an unreasonable choice.

Cholinesterase inhibitors are approved for treatment of mild to moderate dementia, and memantine is approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe Alzheimer disease. Patients with mild vascular dementia have shown mild benefit from memantine. However, memantine use in mild Alzheimer disease has not been well studied. Major contraindications of cholinesterase inhibitors and memantine include, but are not limited to, uncontrolled asthma, angle-closure glaucoma, the sick sinus syndrome, and left bundle-branch block.

See the original guideline document for recommendations for further research.

Definitions:

This guideline grades the evidence and recommendations by using the American College of Physicians' clinical practice guidelines grading system adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

American College of Physicians' Clinical Practice Guidelines Grading System*		
Quality of Evidence	**Strength of Recommendation**	
	Benefits Clearly Outweigh Risks and Burden **OR** Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I recommendation	

*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate pharmacologic treatment of dementia based on tolerability, adverse effect profile, ease of use, and cost of medications

POTENTIAL HARMS

Adverse Effects of Medications

- **Donepezil**: Withdrawal rates because of adverse events associated with donepezil ranged from 0% to 57% in the treatment groups (0% to 20% in placebo groups). No study showed a statistically significant difference between the treatment and placebo groups for serious adverse events except for the expected side effects of cholinesterase inhibitors (diarrhea, nausea, and vomiting). Six studies reported a dose-response effect with increasing frequency of adverse events as dosage increased.
- **Galantamine**: Withdrawal for adverse events for galantamine ranged from 8% to 54% in the treatment group (4% to 17% in the placebo group). Four studies showed a dose-response relationship for adverse events during titration. Although most trials did not report statistical analysis of adverse effects, 2 studies reported statistically significant weight loss in the treatment group. Commonly reported adverse effects included gastrointestinal symptoms (nausea, vomiting, and diarrhea), eating disorders/weight loss, and dizziness.
- **Rivastigmine**: Withdrawal rates related to adverse events ranged from 12% to 29% in the treatment group (0% to 11% in the placebo group). The frequency of adverse events between treatment and control groups did not differ. However, 2 studies showed a dose-response relationship for adverse events. The types of adverse events were consistent with those related to cholinesterase inhibitor use and included dizziness, nausea, vomiting, eating disorder/weight loss, and headache.
- **Tacrine**: The withdrawal rate related to adverse events ranged from 0% to 55% in the treatment group (0% to 12% in the placebo group). The evidence showed that adverse events related to tacrine were serious and increased with higher doses. Elevated alanine aminotransferase level and other hepatic abnormalities were reported in 6 of 7 studies. Nausea, vomiting, gastrointestinal problems, and dizziness were reported in addition to the serious liver abnormalities.
- **Memantine**: The withdrawal rates related to adverse effects varied from 9% to 12% in the treatment group (7% to 13% in the placebo group), including nausea, dizziness, diarrhea, and agitation.

Refer to the original guideline document for more information on adverse effects of medications.

CONTRAINDICATIONS

CONTRAINDICATIONS

Major contraindications of cholinesterase inhibitors and memantine include, but are not limited to, uncontrolled asthma, angle-closure glaucoma, the sick sinus syndrome, and left bundle-branch block.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment.
- The authors of this guideline are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Qaseem A, Snow V, Cross JT Jr, Forciea MA, Hopkins R Jr, Shekelle P, Adelman A, Mehr D, Schellhase K, Campos-Outcalt D, Santaguida P, Owens DK, American College of Physicians/American Academy of Family Physicians Panel on Dementia. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008 Mar 4;148(5):370-8. [63 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Mar

GUIDELINE DEVELOPER(S)

American Academy of Family Physicians - Medical Specialty Society
American College of Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Physicians
American Academy of Family Physicians

GUIDELINE COMMITTEE

Joint American College of Physicians/American Academy of Family Physicians Panel on Dementia

Clinical Efficacy Assessment Subcommittee and the Commission on Science of the American Academy of Family Physicians

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Honoraria: P. Santaguida (American College of Physicians). *Grants received*: V. Snow (Centers for Disease Control and Prevention, Novo Nordisk, Bristol-Myers Squibb, Robert Wood Johnson Foundation, Boehringer-Ingelheim, Endo Pharmaceuticals)

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American College of Physicians (ACP) Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008 Mar 4;148(5):379-397. Electronic copies: Available from the Annals of Internal Medicine Web site.
- Drug treatment for patients with dementia. Continuing medical education (CME) course. Available from the Annals of Internal Medicine Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

PATIENT RESOURCES

The following is available:

- Drug treatment for patients with dementia: American College of Physicians and American Academy of Family Physicians recommendations. Ann Intern Med 2008 Mar 4;148(5):I-141. Electronic copies: Available from the Annals of Internal Medicine Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on April 18, 2008. The information was verified by the guideline developer on May 9, 2008.

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